Listing of Claims

1. (Currently Amended) A method of creating a pure clinical reference solution for testing multiple genetic conditions, wherein the clinical reference solution is substantially free of clinically irrelevant nucleic acid detrimental to the testing, comprising:

determining one or more clinically relevant sites on one or more nucleic acid sequences;

for each clinically relevant site, designing an arrangement of bases to emulate the clinically relevant site as isolated from adjacent clinically irrelevant nucleic acid, wherein the arrangement of bases also includes one or more primer targets;

synthesizing, base by base, a single-stranded artificial version of each arrangement of bases associated with each clinically relevant site; and

~~one or more nucleic acid sequences, each relevant for use as a clinical reference~~

mixing each artificial version of a clinically relevant site into a single solution.

~~; tagging at least one end of each sequence for amplification by a primer; and amplifying the one or more nucleic acid sequences using the primer.~~

2. (Currently Amended) The method as recited in claim 1, wherein each clinically relevant site comprises a mutation of a normal

human nucleic acid sequence, each mutation representing a human genetic condition.

~~the tagging includes attaching an additional sequence of nucleotides, wherein the additional sequence is complementary or identical to a nucleotide sequence of the primer.~~

3. (Cancelled)

4. (Currently Amended) The method as recited in claim 1, wherein:

the synthesizing one or more primer targets ~~tagging~~ includes attaching a first sequence of nucleotides base by base to a first end of each of the one or more synthesized arrangements of bases ~~nucleic acid sequences~~, wherein the first sequence is complementary to a nucleotide sequence of a first primer of a primer set, and

the synthesizing one or more primer targets ~~tagging~~ includes attaching a second sequence of nucleotides base by base to a second end of each of the one or more synthesized arrangements of bases ~~nucleic acid sequences~~, wherein the second sequence is identical to a nucleotide sequence of a second primer of a primer set.

5. (Currently Amended) The method as recited in claim 1, wherein the synthesizing comprises synthesizing, base by base, two complementary ~~nucleic acid~~ strands, wherein:

a first strand includes an artificial version of one of the clinically relevant sites ~~a first nucleic acid sequence relevant for clinical reference~~ and a nucleic acid tag complementary to a first primer of a primer set and

a second strand is ~~includes a nucleic acid sequence~~ complementary to the first strand and to a nucleic acid tag complementary to a second primer of a primer set.

6. (Canceled)

7. (Currently Amended) The method as recited in claim 1, wherein designing an arrangement of bases includes ~~at least one of the one or more synthesized nucleic acid sequences includes at least one~~ recreating a site of a mutation of a nucleotide in a normal human nucleic acid, exclusive of extraneous nucleic acid material adjacent to the site of the mutation.

8. (Currently Amended) The method as recited in claim 1, ~~further comprising synthesizing multiple mixtures of at least one reference nucleic acid apiece,~~ wherein:

each of the artificial versions of a clinically relevant site ~~multiple mixtures~~ has an associated primer set, and wherein:

the reference solution is tuned for a specific battery of clinical tests by differentially amplifying the different clinically relevant sites to different concentrations in the reference solution.

~~each member of one of the multiple mixtures includes a first tag attached to a first end of the member, wherein:~~

~~the first tag comprises a sequence of nucleotides complementary to a nucleotide sequence of a first primer of the associated primer set, and~~

~~each member includes a second tag attached to a second end of the member, wherein:~~

~~the second tag comprises a sequence of nucleotides identical to a nucleotide sequence of a second primer of the associated primer set.~~

9. (Currently Amended) The method as recited in claim 8, wherein different groups of the artificial versions of the clinically relevant sites in the reference solution have associated primer sets such that each different group of clinically relevant sites is amplified independently.

~~further comprising combining each of the multiple mixtures with each other and separately controlling each of the multiple mixtures to achieve separate amounts of amplification for each of the multiple mixtures components.~~

10. (Canceled)

11. (Currently Amended) The method as recited in claim 9, wherein independently amplifying ~~separately controlling~~ each of the groups of clinically relevant sites ~~multiple mixtures~~ includes controlling a physical characteristic of the reference solution ~~a combined mixture of the multiple mixtures~~ to favor an amplification capability of one primer set over an amplification capability another primer set.

12-15. (Canceled)

16. (Currently Amended) The method as recited in claim 1, further comprising adding normal human nucleic acid to the base by base synthesized artificial versions of the clinically relevant sites ~~one or more synthesized nucleic acid sequences relevant for clinical reference~~ in order to achieve a mixture of the nucleic acids in the reference solution representing at least a segment of homologous heterozygous alleles.

17-20. (Canceled)

21. (Currently Amended) The method as recited in claim 1, further comprising joining two parts of one of the arrangements of bases together ~~multiple nucleic acid segments~~ using a ligation extension to perform the synthesizing of a large arrangement of bases. ~~one or more reference nucleic acid sequences.~~

22. (Currently Amended) The method as recited in claim 21, further comprising using a bridge nucleic acid to join multiple parts of the arrangement of bases.

~~wherein for at least one of the reference nucleic acids, the synthesizing includes:~~

~~synthesizing a first nucleic acid that includes a first end comprising a base sequence complementary to the base sequence of the first primer and a second end complementary to a base sequence on a first end of a bridge nucleic acid;~~

~~synthesizing a second nucleic acid that includes a first end comprising a base sequence that matches the base sequence of the second primer and a second end complementary to a second end of the bridge nucleic acid; and~~

~~making the reference nucleic acid by joining multiple nucleic acid segments in the ligation extension, including joining the first nucleic acid on one end of the joined segments using the bridge nucleic acid and joining the second nucleic acid on the opposite end of the joined segments using the bridge nucleic acid.~~

23. (Currently Amended) The method as recited in claim 1, further comprising joining ~~multiple nucleic acids~~ using an overlap extension to join multiple parts of the arrangement of bases.

~~perform the synthesizing one or more reference nucleic acid sequences.~~

24-50. (Canceled)

51. (Withdrawn) A tagged reference nucleic acid for a polymerase chain reaction amplification, comprising:

a synthesized reference nucleic acid having a base sequence capable of being used as a reference;

a first nucleic acid tag bound to a first end of the synthesized reference nucleic acid, wherein the first nucleic acid tag has a base sequence complementary to a base sequence of a first primer of a primer set; and

a second nucleic acid tag bound to a second end of the synthesized reference nucleic acid, wherein the second nucleic acid tag has a base sequence matching a base sequence of a second primer of the primer set.

52. (Withdrawn) The tagged reference nucleic acid as recited in claim 51, wherein the synthesized reference nucleic acid includes a base sequence representing a mutation of a gene.

53. (Withdrawn) The tagged reference nucleic acid as recited in claim 52, wherein the gene comprises a cystic fibrosis transmembrane conductance regulator gene.

54-70. (Canceled)

71. (Currently Amended) A method, comprising:

designing multiple reference nucleic acids, wherein each reference nucleic acid comprises an arrangement of bases emulating a clinically relevant site of a human nucleic acid exclusive of clinically irrelevant human nucleic acid adjacent to the clinically relevant site;

synthesizing, base by base for each reference nucleic acid, a first mixture of various of the reference nucleic acids, wherein each of the various reference nucleic acids in the first mixture includes one or more tags allowing PCR amplification of the first mixture via a primer set specific to the tags of the first mixture; and

synthesizing, base by base for each reference nucleic acid, a second mixture of various of the reference nucleic acids, wherein each of the various reference nucleic acids in the second mixture includes one or more tags allowing PCR amplification of the second mixture via a second primer set specific to the tags of the second mixture.

72. (Original) The method as recited in claim 71, further comprising combining the first and second mixtures to make a single mixture and differentially amplifying the first mixture and the second mixture in a PCR reaction by controlling amounts of the first primer set and the second primer set in the single mixture.

73. (Original) The method as recited in claim 72, wherein at least some of the reference nucleic acids include mutations of a normal human nucleic acid.

74. (Original) The method as recited in claim 73, further comprising adding normal human nucleic acid to the single mixture to obtain heterozygous pairs, wherein each heterozygous pair includes a normal segment of human nucleic acid and a mutated copy of the normal segment of human nucleic acid.